REMARKS

Applicants have canceled claims 12, 13, 14, 39, and 49 without prejudice and expressly reserve the right to pursue the subject matter of the canceled claims in one or more subsequent applications.

Applicants have amended claims 15, 17, 19, 38, and 40 to recite "cells capable of producing an angiogenic factor", and that the cells are injected intramyocardially into normal tissue "adjacent to ischemic tissue". Support for the foregoing amendments is found. e.g., on page 3, line 22 to page 4, line 2, and original claims 23 and 39, which recite the "delivery site" for the cells, i.e., into normal tissue adjacent to ischemic tissue and claims.

Applicants have also amended claims 51 and 54 to recite the proper claim dependency.

Claims 12-13 stand rejected under the judiciously created doctrine of obviousness-type double patenting as being purportedly unpatentable over claims 31 and 35 of co-pending application number 10/623,205. Applicants have canceled claims 12 and 13 without prejudice thereby rendering this rejection moot.

Claims 15, 17, 19 and 23-25 stand rejected under 35 U.S.C. 112, second paragraph for purportedly being indefinite. The Examiner contends that all cells are capable of producing an angiogenic factor. Applicant disagrees with the Examiner's remarks. Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims 35 U.S.C. 112, second paragraph.

Claims 15, 17, 19 and 23-25 stand rejected under 35 U.S.C. 112, second paragraph for purportedly being indefinite. The Examiner contends that all cells are capable of producing an angiogenic factor and states "this rejection is made because the metes and bounds of the limitation are not clear to the Examiner."

The Examiner states that applicant has not claimed a cell, but instead that a subset of cells which are capable of producing an angiogenic factor and. However, applicant is not claiming a "cell" or "a subset of cells", rather applicant is claiming methods to stimulate collateral blood vessel formation in the myocardium, to induce angiogenesis in the myocardium, to improve contractile function of an ischemic heart, or for treating ischemia, all of which comprise the step

of administering cells, capable of producing an angiogenic factor, to the myocardial tissue. Applicant has provided examples of cells that can be administered e.g., endothelial progenitor cells, cardiac myoblasts, mononuclear cells, bone marrow stromal cells and stem cells and has disclosed that the cells may be primary cells or expanded ex vivo or genetically engineered (see specification page 9, lines 17-26). Thus the term is amply described in the specification and leaves no doubt over its meaning to those skilled in the art. Thus one of skill in the relevant art would readily understand that the claimed methods include a step of delivering "cells capable of producing an angiogenic factor" to the myocardium and would readily appreciate which cells would fall within that meaning.

The examiner's approach to determining whether appellants' claims satisfy the requirements of § 112 appears to have been to study appellants' disclosure, to formulate a conclusion as to what the examiner regards as the broadest invention supported by the disclosure, and then to determine whether appellants' claims are broader than the examiner's conception of what "the invention" is. § 112 does not permit such an approach to claims. The first sentence of the second paragraph of § 112 is essentially a requirement for precision and definiteness of claim language. If the scope of subject matter embraced by a claim is clear, and if the applicant has not otherwise indicated that he intends the claim to be of a different scope, then the claim does particularly point out and distinctly claim the subject matter which the applicant regards as his invention. *In re Borokowski* 164 USPQ 642 (1970) In view of the foregoing remarks, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims 35 U.S.C. 112, second paragraph.

Claims 12-14, 15, 17, 19, 23-25, 38, 39, 40 and 49-51 stand rejected under 35 U.S.C. 112, first paragraph for purportedly being non-enabled. In view of the amendments to the claims and the following remarks, applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

Applicant has canceled claims 12-14, 39, and 49 without prejudice and as such has obviated this rejection as it pertains to these claims.

Regarding the remaining claims, the Examiner contends that applicant's invention is non-enabled because: the injected cells must engraft to achieve their effect; that immune responses

would be expected for any non-autologous therapy; that the injected cells become part of the tissue into which they are injected and replace ischemic tissue and that the skilled artisan would not reasonably predict that the cells injected into another site, even adjacent could become part of and replace the ischemic tissue; that targeting tissues and doing so in large enough numbers is not predictable, and; that delivery of adenovirus vectors to the pericardium, which the Examiner contends is next to ischemic tissue, does not improve myocardial collateral perfusion. The Examiner also contends that the Examples have nothing to do with the administration of cells and the artisan would not reasonably predict that any particular cell type could engraft into the myocardium, much less express an angiogenic transgene for long enough period to effect treatment without being removed by immune responses (Office Action pages 7-13). The Examiner cites Cutler et al. 2001 Stem Cells 19:108-117, Pittenger et al., US Patent 6,387,369, filed 1999, Lazarous (1999) Cardiovascular Research 44 and Holden et al. (2002) Science 296:2126-29 and Orkin et al. (2002) Nature Immunology 3(4):323-28 to support his position. Applicant respectfully disagrees.

Regarding the Examiner's contentions that the cells of applicant's claims must engraft to achieve a desired effect, those of skill in the art appreciate that cell engraftment is NOT a prerequisite for achieving a desired effect. For example, applicant directs the Examiner's attention to the reviews by Pittenger and Martin, ("Mesenchymal Stem Cells and Their Potential as Cardiac Therapeutics," Circulation Research, (July 9, 2004) pp. 9-20)(enclosed) and Kinnaird et al. ("Marrow-Derived Stromal Cells Express Genes Encoding a Broad Spectrum of Arteriogenic Cytokines and Promote In Vitro and In Vivo Arteriogenesis Through Paracrine Mechanisms, Circulation Research (March 19, 2004) pp: 678-685)(enclosed). Pittenger and Martin states:

> Recent data from Kinnaird et al. suggests that the mechanism of MSC-mediated improvements in perfusion may reside ***in their ability to secrete a variety of angiogenic cytokines*** ... many of which are upregulated in hypoxia. (page 15, right Col. last sentence of section entitled "MSC Role in Angiogenesis") (emphasis added)

and the review by Kinnaird et al. states:

> "The ability of bone marrow cells to secrete multiple arteriogenic cytokines has led to several studies demonstrating these cells enhance collateral flow, and the responsible mechanism has often been ascribed to these cells incorporating into the developing collaterals. However, the actual magnitude of incorporation in bone marrow-derived cells into vascular structures varies substantially among studies. Although some studies report over 50% of capillaries containing transplanted cells, other studies have reported only occasional positive vessels despite noting impressive improvements in perfusion. Taken together, these data suggest that other mechanisms ***apart from cell incorporation*** may contribute to collateral remodeling observed after marrow-derived cell therapy in various models of ischemia." (paragraph spanning, page 682-683) (emphasis added).

Applicant's claims do not require the cells to engraft and these reviews demonstrate that engraftment of injected cells is not a prerequisite of obtaining the desired effect. As such, one of skill in the art, with applicants' specification in hand, would reasonably expect that the administration of cells that express angiogenic factors to the normal tissue of an ischemic heart would be efficacious, regardless of whether or not they engraft in the injected tissue.

Regarding the Examiner's statements relating to allogeneic and xenogenic cells inducing an immune response, e.g.,:

> "...the Artisan would further conclude that such immune responses would be expected for any non-autologous therapy as it is well known in the art that allogenic and xenogenic cells also induce immune responses." (Office Action, page 10).

Applicants respectfully disagree and direct the Examiner's attention to Henning et al. ("Human umbilical cord blood mononuclear cells for the treatment of acute myocardial infarction", Cell Transplan 2004; 13(7-8): 729-39). Henning et al. states "the present experiments demonstrate that [human umbilical cord blood mononuclear progenitor cells] substantially reduce infarction size in rats without requirements for immunosuppression." See also, Pittenger and Martin, *supra*, page 13 left col., which states:

> "Intuitively, one might expect allogeneic MSCs (allo MSCs) would stimulate T cell proliferation and that donor MSCs would be recognized by responder T cells and rejected by a recipient host. However, experimental evidence indicates this might not be the case. MSCs have been shown to inhibit T cell proliferation in several laboratories."

Applicant has demonstrated that adenovirus vectors delivered to the heart express the angiogenic factor in the heart for a period long enough to achieve the effects recited in the claims. Thus the ordinary skilled artisan based on such data would expect that cells expressing an angiogenic factor would also continue to express the angiogenic factor when delivered to the heart for a period long enough to achieve the effects recited in the claims, prior to being removed by an immune response, if such an immune response was indeed induced.

Regarding the Examiner's contention that the skilled artisan would not reasonably predict that the cells injected into another site, even an adjacent site, could become part of and replace the ischemic tissue, the foregoing reviews by Pittenger and Martin and Kinnaird et al. demonstrate that engraftment is not a prerequisite for achieving a desired result. Furthermore, applicants have demonstrated that achieving expression of an angiogenic factor in tissue adjacent to ischemic tissue increases capillary density, blood flow and contractive wall function (See Examples). As such one of skill in the art would reasonably predict the efficacy of applicant's claimed methods.

In addition, those of skill in the art would expect that cells can be delivered directly to the heart target tissue by any well known method in the art. For example, Applicants have disclosed that the cells may be delivered e.g., via catheters (see e.g. page 12, lines 18 to 28) and Prittenger US Patent 6,387,369, column 4, lines 49-64 and col. 5, lines 38-39 e.g., demonstrate the direct injection of MSCs into the heart. It would require routine experimentation to deliver sufficient amounts of the cells producing an angiogenic factor to the target tissue to achieve the desired result. It is not fatal if some experimentation is needed because the patent document is not intended to be a production specification. *Northern Telecom, Inc., v. Datapoint Corp* 15 USPQ 2d 1321 (Fed Cir. 1990)

The Examiner also states:

> "other than the use of stem cells, the Examiner fails to find any reason to expect that any other organ's cell would even produce an effect. For example, why would anyone believe that a brain cell would be efficacious in treating an ischemic heart? If there is some logic to this the Examiner requests explanation."
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> (Office Action page 11).

An application is drafted for those of skill in the art and a certain level of competence is accorded such persons. It is not a function of the enablement requirement of 35 U.S.C. 112, to specifically exclude possible inoperative substances see *Atlas Powder Co. v EI du Pont de Nemours & Co.* 224 USPW 409 (Fed Cir 1984) citing *In re Dinh-Nguyen*, 181 USPQ 46, 48 (CCPA 1974). Rather enablement is satisfied if applicants have provided sufficient guidance for one of skill in the art to practice the invention. A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art , using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation. In addition, it is not fatal if some experimentation is needed, for the patent document is not intended to be a production specification. *Northern Telecom, Inc., v. Datapoint Corp* 15 USPQ 2d 1321 (Fed Cir. 1990) Applicant's amended claims recite a number of cell types that are useful in this invention and applicant has identified a variety of angiogenic factors that are useful in this invention, as well as various methods for delivering the cells to the myocardium and has demonstrated that the expression of the angiogenic factor, VEGF165 in normal tissue of an ischemic heart results in, e.g., increased blood flow, capillary density and wall motion (page 14, lines 4-9 and page 15, lines 1-17). As such, one of skill in the art provided with applicant's specification and the knowledge generally available in the art could readily practice the invention, which comprises intramyocardially delivering cells capable of producing an angiogenic factor to normal tissue adjacent to ischemic tissue in an ischemic or diseased heart in an amount sufficient to stimulate collateral blood vessel formation, induce angiogenesis, improve contractile function, and ameliorate the symptoms of ischemia without undue experimentation.

Regarding the Examiner's remarks that the examples have nothing to do with the administration of cells, applicant has demonstrated that rAAV expressing an angiogenic factor

injected into normal myocardial tissue expresses its recombinant protein at sufficient levels to induce angiogenesis, improve contractile function, or stimulate collateral blood vessel formation in the ischemic or diseased heart. Based on this knowledge, one of skill in the art would expect that cells producing an angiogenic factor, particularly VEGF, would also continue to express the angiogenic factor once injected into normal tissue adjacent to ischemic tissue and would produce the results applicant achieved using a recombinant AAV. It would not require undue experimentation for one of skill in the art to determine an amount of cells that would be sufficient to ameliorate the symptoms of ischemia, induce angiogenesis, improve contractile function, or stimulate collateral blood vessel formation in said ischemic or diseased heart.

The Examiner has requested a further explanation of Example 2, in particular the Examiner states:

> Example 2 also argues that such administration provides for better wall motion; however, the results "indicate trends towards improvement in wall motion" (p. 15, paragraph 2). How this relates to the invention, and how these results demonstrate improved wall motion are unclear. The Examiner requests further explanation if Applicant wishes to use this information to support their claims.
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> (Office Action page 8-9).

The dobutamine stress echocardiography disclosed in Example 2 is a well-established means for the diagnosis of myocardial abnormalities and is based on the visual detection of ischemia-induced radial wall motion abnormalities. Those of skill in the art appreciate that improvements in wall motion are indicative of a less stiff more compliant ventrical and thus an improvement in heart function. Applicants direct the Examiner's attention to the review by Pittenger and Martin *supra*, page 15-16, which also discuss improvements in wall motion as an indication of improvements in an infarcted heart. Claim 19 claims a method to increase contractile function of an ischemic heart. Improved wall motion correlates with increased contractile function in the heart. As such, one of ordinary skill in the art presented with data demonstrating increased wall motion would readily understand this to be a measure of increased contractile function. Applicants direct the Examiner's attention to Figure 7, which depicts the regional wall motion scores on dobutamine stress echocardiography.

In view of the foregoing remarks and amendments to the claims, applicant requests that the Examiner reconsider and withdraw the rejection of the claims for purported lack of enablement. Applicant believes the pending application is in condition for allowance and respectfully requests that it be passed to issue.

Applicant believes no additional fees are due with this response. However, if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. WO-BSX 236 US2/10409073 from which the undersigned is authorized to draw.

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Respectfully submitted,

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